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Systematic evaluation of pembrolizumab dosing in patients with advanced non-small-cell lung cancer

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Background: In the phase I KEYNOTE-001 study, pembrolizumab demonstrated durable antitumor activity in patients with advanced non-small-cell lung cancer (NSCLC). We sought to characterize the relationship between pembrolizumab dose, exposure, and response to define an effective dose for these patients.

Patients and methods: Patients received pembrolizumab 2 mg/kg every 3 weeks (Q3W) (*n* = 55), 10 mg/kg Q3W (*n* = 238), or 10 mg/kg Q2W (*n* = 156). Response (RECIST v1.1) was assessed every 9 weeks. The relationship between the estimated pembrolizumab area under the concentration–time curve at steady state over 6 weeks ($AUC_{ss-6weeks}$) and the longitudinal change in tumor size (sum of longest diameters) was analyzed by regression and non-linear mixed effects modeling. This model was simultaneously fit to all tumor size data, then used to simulate response rates, normalizing the trial data across dose for prognostic covariates (tumor PD-L1 expression and *EGFR* mutation status). The exposure–safety relationship was assessed by logistic regression of pembrolizumab $AUC_{ss-6weeks}$ versus occurrence of adverse events (AEs) of interest based on their immune etiology.

Results: Overall response rates were 15% [95% confidence interval (CI) 7%–28%] at 2 mg/kg Q3W, 25% (18%–33%) at 10 mg/kg Q3W, and 21% (95% CI 14%–30%) at 10 mg/kg Q2W. Regression analyses of percentage change from

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baseline in tumor size versus $AUC_{ss-6weeks}$ indicated a flat relationship (regression slope $P > 0.05$). Simulations showed the exposure–response relationship to be similarly flat, thus indicating that the lowest evaluated dose of 2 mg/kg Q3W to likely be at or near the efficacy plateau. Exposure–safety analysis showed the AE incidence to be similar among the clinically tested doses.

Conclusions: No significant exposure dependency on efficacy or safety was identified for pembrolizumab across doses of 2–10 mg/kg. These results support the use of a 2 mg/kg Q3W dosage in patients with previously treated, advanced NSCLC.

ClinicalTrials.gov registry: NCT01295827.

Key words: exposure–response, immunotherapy, non-small-cell lung cancer, pembrolizumab, PD-L1, tumor size modeling

introduction

Pembrolizumab is a potent, highly selective, humanized IgG4 monoclonal antibody against the immune checkpoint programmed death 1 (PD-1) that has a binding affinity for the PD-1 ligands PD-L1 and PD-L2 in the low nanomolar concentrations [PD-L1 half-maximal inhibitory concentration (IC_{50}), ∼0.1–0.3 nM and PD-L2 IC_{50}, ∼0.5–0.9 nM]. Consistent with other monoclonal antibodies, pembrolizumab has a low clearance (0.2 l/day), limited central (3.7 l) and peripheral (4.4 l) volume of distribution, and low to moderate variability (22%–41%) [1–3]. The half-life is 14–22 days, and serum exposure appears linear over the range of 0.1–10 mg/kg at steady-state dosing. Pembrolizumab has demonstrated robust antitumor activity and manageable toxicity across multiple dosages in several advanced malignancies. Pembrolizumab 2 mg/kg every 3 weeks (Q3W) was approved through the US Food and Drug Administration accelerated approval program for previously treated, PD-L1-positive advanced non-small-cell lung cancer (NSCLC). A pooled analysis of the first 495 patients with previously treated or treatment-naive advanced NSCLC enrolled in the multicohort phase Ib KEYNOTE-001 study (ClinicalTrials.gov identifier, NCT01295827) demonstrated acceptable toxicity and durable antitumor activity for pembrolizumab, the magnitude of which was dependent on tumor PD-L1 expression [4].

We present an integrated analysis including efficacy and safety data from the final NSCLC expansion cohort of KEYNOTE-001. This final cohort, which included patients with previously treated NSCLC who received pembrolizumab 2 mg/kg Q3W only, was excluded from the initial publication by Garon et al. [4] because it was not part of the planned training or validation sets for PD-L1 expression. We also describe a comprehensive exposure-response model based on tumor size data that was developed using all available NSCLC data from KEYNOTE-001 and employed for pembrolizumab dose selection in advanced NSCLC. This approach has become increasingly common for evaluating growth dynamics and treatment response in oncology [5–7] and is well suited for integrating and normalizing data from different time points and treatment durations.

methods

study design

KEYNOTE-001 is a multicenter, open-label, phase Ib trial that included multiple advanced NSCLC expansion cohorts. Eligibility criteria for the first 495 patients enrolled were reported previously [4]. Key eligibility criteria for the final cohort included age ≥18 years, locally advanced or metastatic NSCLC, disease progression after platinum-based chemotherapy and an appropriate tyrosine kinase inhibitor for a sensitizing *EGFR* mutation or *ALK* translocation if present, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, PD-L1 positivity, adequate organ function, no history of pneumonitis, and no systemic immunosuppressive therapy or active autoimmune disease.

All patients provided written informed consent. The study was conducted in accordance with the protocol, good clinical practice standards, and the Declaration of Helsinki. All protocols and amendments were approved by the appropriate institutional review board or ethics committee at each participating institution.

treatment and assessments

In the initial KEYNOTE-001 NSCLC cohorts, 489 of 495 patients received pembrolizumab 10 mg/kg Q3W or 10 mg/kg every 2 weeks (Q2W); the final six patients received pembrolizumab 2 mg/kg Q3W before the protocol was amended [4]. Based on data from a randomized comparison in melanoma showing no difference between pembrolizumab 2 and 10 mg/kg Q3W [8], a final NSCLC cohort was added in which patients received pembrolizumab 2 mg/kg Q3W. Patients received pembrolizumab until disease progression assessed per immune-related response criteria [9] by investigator review, intolerable toxicity, or investigator or patient decision. Dose delay, prolonged dosing interval, or discontinuation were used to manage toxicity; dose reduction was not allowed. Tumor lesions were measured using computed tomography or magnetic resonance imaging at baseline and every 9 weeks thereafter. Tumor size was recorded as the sum of the longest diameters (SLD) assessed per RECIST v1.1 [10] by independent central review. Adverse events (AEs) were collected throughout the study and for 30 days after treatment discontinuation (90 days for serious AEs) and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. AEs of special interest based on immune etiology ('immune-mediated AEs') were identified from a prespecified list of terms (supplementary Table S1, available at *Annals of Oncology* online) and reported regardless of attribution to treatment by the investigator.

PD-L1 expression was assessed in contemporaneous biopsy samples using immunohistochemistry and the 22C3 anti-human PD-1 antibody (Merck & Co., Inc.) [4]. For enrollment, expression was prospectively assessed using a prototype assay, with positivity defined as membranous staining on ≥1% of cells within tumor nests or staining in stroma. The PD-L1 tumor proportion score (TPS), defined as the percentage of tumor cells with membranous PD-L1 staining, was retrospectively assessed using a clinical trial assay, with positivity defined as TPS ≥1%. Based on the findings by Garon et al. [4], PD-L1 positivity was further categorized as TPS 1%–49% or ≥50%.

Blood samples (3.5 ml) for peak and trough pharmacokinetic assessment were collected regularly throughout treatment (Supplementary Materials, available at *Annals of Oncology* online). Regardless of treatment schedule, samples were collected at baseline and week 6. Pembrolizumab serum concentration was assessed using an electrochemiluminescence-based immunoassay with a 10 ng/ml limit of quantitation.

exposure-efficacy analysis

A tiered evaluation approach was employed as part of a comprehensive evaluation, starting with more traditional comparisons of observed efficacy data (exploratory regression analyses) and followed by non-linear mixed effects (NLME) modeling. Data analysis conducted in a stratified manner for the early analyses was pooled for the NLME model of change from baseline in tumor size because the model's statistical framework was better suited for integrating data.

All patients who had pharmacokinetic data and measurable disease per RECIST v1.1 by central review at baseline were included in the exposure-efficacy regression and NLME modeling analyses ($n = 496$: $n = 6$ treatment-naive and 47 previously treated patients received 2 mg/kg Q3W, $n = 45$ treatment-naive and 216 previously treated received 10 mg/kg Q3W, and $n = 39$ treatment-naive and 143 previously treated received 10 mg/kg Q2W). Exposure was defined as the area under the concentration–time curve at steady state over 6 weeks ($AUC_{ss-6weeks}$), derived from an independent population pharmacokinetic model (manuscript submitted for publication). $AUC_{ss-6weeks}$ was chosen as the exposure metric because it provided an integer number of dosing intervals across Q2W and Q3W regimens; steady state was selected for convenience and because pembrolizumab exhibits linear pharmacokinetics. A common steady-state exposure metric was used to avoid potential confounding between early study drop-out unrelated to dose/pharmacokinetic variability and cumulative exposure (i.e. patients who progressed early and discontinued treatment ultimately had lower total exposure to pembrolizumab than those treated for a longer duration). Such a correlation could artificially manifest as a positive exposure–response relationship if a time-dependent exposure metric was chosen. Moreover, because pembrolizumab exhibits linear and time-independent pharmacokinetic behavior, $AUC_{ss-6weeks}$ was expected to be a reasonable proxy exposure for all patients (e.g. those who had lower $AUC_{ss-6weeks}$ are expected to have proportionally lower $AUC_{0-anytime}$ earlier during treatment).

Efficacy was defined as change from baseline in the SLD of target lesions (i.e. tumor size). Change in tumor size was considered an appropriate efficacy measure given the demonstrated relationship between changes in tumor size and overall survival in NSCLC [5, 11, 12]. Before NLME modeling, an exploratory regression analysis was carried out to evaluate observed change in SLD versus pembrolizumab exposure at a single post-baseline time point. Particular emphasis was placed on weeks 18 and 27 because at the time of analysis, these were the latest common imaging time points reached by the majority of patients remaining on study who were treated at 2 and 10 mg/kg.

tumor size NLME model structure

All tumor size data were used simultaneously to fit the NLME model. At 2 mg/kg, the majority of data were up to 18 weeks of follow-up, although six patients were observed for >1 year; together with the 10 mg/kg dose groups, these data were used to inform long-term model behavior.

The tumor size model is illustrated in supplementary Figure S1, available at *Annals of Oncology* online and is described mathematically as

$$Tumor\ size = Baseline \times [(1 - f) \times e^{k_{growth} \times time} +$$
$$f \times e^{-k_{death} \times max(0,\ time-delay)}]$$

where 'Baseline' is the actual measured tumor size (SLD) at initial screening, k_{growth} the first-order tumor growth rate, k_{death} the rate constant that captures the kinetics of net removal in the responding portion of the tumor, and 'delay' the delay between baseline and the first dose. Both k_{growth} and k_{death} were constrained to be positive during estimation, with individual parameters log normally distributed.

A fraction (f) of total tumor diameter was assumed to be accessible to treatment, with the remaining portion ($1-f$) undergoing exponential growth. This model parameterization is similar to previous models in the

literature and was sufficiently flexible to capture different patterns of tumor growth observed for NSCLC, as well as for many other solid tumors in pembrolizumab-treated patients.

To account for the effect of drug exposure, $AUC_{ss-6weeks}$ was incorporated into the structural model parameterization on the tumor kill rate by assuming a log-linear relationship:

$$k_{death} = TVk_{death} \times \left(\frac{AUC_{ss-6\,weeks}}{AUC_{typical,ss-6\,weeks}} \right)^{\theta}$$

Results from the independent population pharmacokinetics model provided *post hoc* clearance (CL) estimates, with plasma exposure within the dosing interval at steady state calculated as dose/CL. Here, TVk_{death} denotes the typical value of k_{death} in the population; $AUC_{typical,ss-6weeks}$ (7079 mg/l × day) is used to normalize exposure values. The estimated value of θ determines the extent of the pembrolizumab exposure–response in NSCLC. Only observed tumor sizes were used for the modeling, with no imputations for missing data.

The patient-specific factors of PD-L1 expression level, smoking history, ECOG performance status, demographics (age, sex, and weight), baseline tumor size, prior treatment, and *EGFR* mutation status were tested for inclusion in the model using the stepwise covariate modeling function of PsN [13] (forward inclusion at $P < 0.01$ and backward exclusion at $P < 0.001$). The Supplementary Methods, including supplementary Figures S1–S4 and Tables S2–S6, available at *Annals of Oncology* online, provide further details on the handling of covariates.

trial simulations

Response rate simulations were conducted to normalize for potential data imbalances with respect to covariates and dose/exposure. The expected dose–response relationships based on the modeled exposure-tumor size response were determined using uncertainty simulations based on the final model-estimated parameters. Briefly, 1000 draws were made from the parameter distributions, and for each set of population parameters, a trial with 1000 patients resampled with replacement from the observed dataset at each dose was simulated, accounting for interindividual and residual variability. SLD output from model simulations was categorized as response (SLD reduction from baseline ≥30%), stable disease (change in SLD from baseline between −30% and +20%), and progressive disease (≥20% increase in SLD from baseline); these categories were analogous to standard RECIST v1.1 categories [10] except that non-target and new lesions were not considered when categorizing response. The median and 90% confidence interval (CI) of the proportion of patients in each category were tabulated across the 1000 uncertainty replicate simulations and plotted across the range of doses studied to graphically demonstrate the relationship between tumor size and exposure.

exposure–safety relationship

Patients enrolled in all NSCLC cohorts of KEYNOTE-001 who had pharmacokinetic data were included in an analysis of the relationship between pembrolizumab $AUC_{ss-6weeks}$ and the incidence of immune-mediated AEs. Logistic regression was used to analyze the frequency of immune-mediated AEs.

results

efficacy and safety of pembrolizumab 2 mg/kg Q3W: clinical observations

Between 3 April 2014 and 14 July 2014, 55 patients with previously treated NSCLC received pembrolizumab 2 mg/kg Q3W. Patient characteristics were as expected for a previously treated

Table 1. Overall response and disease control rates per RECIST v1.1 by central review in patients in patients with measurable disease at baseline by central review

| | Pembrolizumab | | |
	2 mg/kg Q3W	10 mg/kg Q3W[a]	10 mg/kg Q2W[a]
ORR, % (95% CI)			
Total[b]	$n = 52$	$n = 155$	$n = 105$
	15 (7–28)	25 (18–33)	21 (14–30)
PD-L1 TPS ≥50%	$n = 23$	$n = 42$	$n = 31$
	30 (13–53)	48 (32–64)	39 (22–58)
PD-L1 TPS 1%–49%	$n = 23$	$n = 49$	$n = 43$
	0 (0–15)	14 (6–27)	14 (5–28)
PD-L1 TPS <1%	$n = 4$	$n = 18$	$n = 9$
	25 (<1–81)	6 (<1–27)	11 (<1–48)
DCR, % (95% CI)			
Total[b]	$n = 52$	$n = 155$	$n = 105$
	50 (36–64)	48 (40–56)	50 (40–60)
PD-L1 TPS ≥50%	$n = 23$	$n = 42$	$n = 31$
	57 (35–77)	60 (43–74)	55 (36–73)
PD-L1 TPS 1%–49%	$n = 23$	$n = 49$	$n = 43$
	48 (27–69)	39 (25–54)	49 (33–65)
PD-L1 TPS <1%	$n = 4$	$n = 18$	$n = 9$
	25 (<1–81)	33 (13–59)	44 (14–79)

CI, confidence interval; DCR, disease control rate; ORR, overall response rate; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TPS, tumor proportion score (i.e. percentage of tumor cells with membranous PD-L1 expression as assessed by a clinical-trial assay).
[a]Includes only patients treated at 10 mg/kg in randomized cohorts with similar inclusion criteria as the 2 mg/kg cohort, including the amount of prior therapy and requirement for PD-L1 positivity per the prototype assay at baseline.
[b]Includes patients for whom a PD-L1 TPS could not be assigned ($n = 2$ for 2 mg/kg and $n = 90$ for 10 mg/kg).

advanced NSCLC population (supplementary Table S7, available at *Annals of Oncology* online). As of the 23 January 2015, data cutoff date, all patients had a minimum follow-up duration of 27 weeks; 15 (27%) patients remained on pembrolizumab. The most common reason for discontinuation was disease progression ($n = 20$; 36%).

The overall response (ORR) and disease control (DCR) rates per RECIST v1.1 by central review were 15% and 50%, respectively, in patients with measurable disease at baseline ($n = 52$) (Table 1). ORR was 30% in patients with PD-L1 TPS ≥50% ($n = 23$), 0% in patients with TPS 1%–49% ($n = 23$), and 25% in patients with TPS <1% ($n = 4$). Decreases from baseline in tumor size were observed for 67% of patients with known PD-L1 expression treated at 2 mg/kg (Figure 1). Among patients treated at 10 mg/kg in randomized cohorts with similar inclusion criteria as the 2 mg/kg cohort, including the amount of prior therapy and requirement for PD-L1 positivity per the prototype assay at baseline, decreases from baseline were observed in 66% of patients treated at Q3W and 63% treated at Q2W (Figure 1); ORR and DCR were similar to those of patients treated with pembrolizumab 2 mg/kg (Table 1).

Treatment-related AEs were reported for 26 (47%) patients treated with pembrolizumab 2 mg/kg Q3W. Five (9%) patients reported grade 3–5 treatment-related AEs ($n = 2$ grade 3 colitis, $n = 1$ grade 5 cardiorespiratory arrest, $n = 1$ grade 4 pneumonitis, and $n = 1$ grade 3 pneumonitis). The treatment-related death occurred in a 75-year-old man who was hospitalized on day 30 for possible pneumonia; 3 days later, he died from cardiopulmonary arrest considered by the investigator to be possibly related to pembrolizumab. Three (5%) patients discontinued treatment because of drug-related AEs ($n = 1$ each grade 5 cardiorespiratory arrest, grade 4 pneumonitis, and grade 3 pneumonitis). Immune-mediated AEs occurred in 9 (15%) patients: colitis ($n = 2$ grade 3, $n = 1$ grade 1), hypothyroidism ($n = 2$ grade 2, $n = 1$ grade 1), pneumonitis ($n = 1$ grade 3, $n = 1$ grade 4), and exfoliative dermatitis ($n = 1$ grade 1). Considering all 550 patients with NSCLC enrolled in KEYNOTE-001, the AE profile observed at 2 mg/kg Q3W was mostly similar to that observed in patients treated at higher dosages (Table 2).

exploratory regression and model-based analyses of the exposure–efficacy relationship

Observed tumor size data showed a wide range of longitudinal response patterns across the previously treated population. At week 18, 170 previously treated patients had both tumor size and exposure data. Exploratory graphical analysis of observed tumor size and exposure data from these patients showed a flat relationship between exposure and change from baseline in tumor size at 18 weeks, with overlapping CIs observed between subsets defined by binned $AUC_{ss–6weeks}$ (Figure 2). The linear regression slope estimates were not significantly different from zero, with P-values greater than the prespecified significance level (>0.05), regardless of whether the data were pooled or stratified by PD-L1 expression (supplementary Figure S5, available at *Annals of Oncology* online).

In agreement with the exploratory graphical and linear regression analyses of the data observed at week 18, individual pembrolizumab exposures (across all patients) also showed no statistically significant influence on the model-estimated tumor shrinkage rate in an NLME analysis of the exposure–response relationship ($P = 0.54$ based on −2 log-likelihood reduction and χ^2 test). The 95% CIs of the exposure response parameter were found to overlap with zero (point estimate, 0.196; range, −0.0784 to 0.47), consistent with no significant difference from a flat exposure–response relationship. PD-L1 expression (Figure 3 and supplementry Table S5, available at *Annals of Oncology* online) and *EGFR* mutation (supplementary Table S5, available at *Annals of Oncology* online) status were the only factors found that explained a significant portion of interindividual variability in longitudinal tumor size patterns, with the impact of these factors found to be independent of dose. (Full details of structural model selection and analysis of covariate effects are found in the Supplementary Materials, available at *Annals of Oncology* online.)

exposure–response simulations

Model-simulated median response rates at week 27 for patients with PD-L1 TPS ≥50% were 39% (90% CI 31%–46%) at 2 mg/kg Q3W, 40% (90% CI 34%–45%) at 10 mg/kg Q3W, and 44%
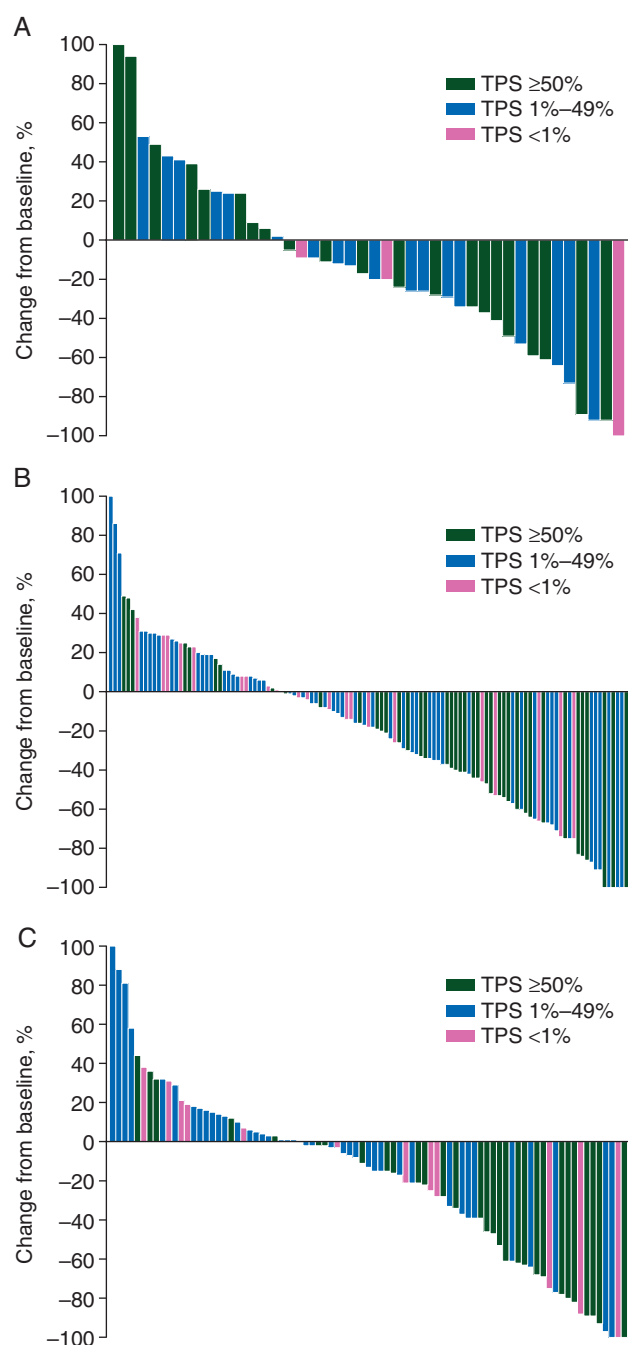
Figure 1. Best percentage change from baseline in sum of the longest diameters of target lesions by PD-L1 TPS. (A) Patients treated with pembrolizumab 2 mg/kg every 3 weeks. (B) Patients treated with pembrolizumab 10 mg/kg every 3 weeks. (C) Patients treated with pembrolizumab 10 mg/kg every 2 weeks. Change from baseline in tumor size was assessed in patients with measurable disease at baseline by RECIST v1.1 per central review and ≥1 evaluable postbaseline tumor assessment who had known PD-L1 TPS. PD-L1, programmed death ligand 1; TPS, tumor proportion score.

exposure–safety relationship

A total of 544 patients were evaluable for the relationship between exposure and safety. Logistic regression analysis identified treatment duration as a significant factor for occurrence of immune-mediated AEs. After inclusion of treatment duration in the model, no significant relationship between pembrolizumab exposure assessed as $AUC_{ss-6weeks}$ and immune-mediated AEs was found ($P = 0.57$) (supplementry Figure S6, available at *Annals of Oncology* online). Similarly, pembrolizumab exposure was not significantly correlated with the hazard for the occurrence of immune-mediated AEs in the time-to-event analysis ($P = 1.0$). Apart from treatment duration, no other investigated covariate was a significant predictor of the probability of experiencing an immune-mediated AE. Based on simulations from the final logistic regression model, even when forcing a relationship with pembrolizumab exposure, the predicted immune-mediated AE incidence at 9 months was similar for 2 mg/kg Q3W (26%), 10 mg/kg Q3W (27%), and 10 mg/kg Q2W (28%).

discussion

Based on the observed clinical data and comprehensive clinical pharmacology modeling and simulation, the approved 2 mg/kg Q3W dose of pembrolizumab provides clinically significant antitumor activity in NSCLC, with an efficacy and safety profile comparable to those observed with doses of 10 mg/kg Q3W or 10 mg/kg Q2W. Given that no dose–exposure–response dependency for efficacy or safety was identified between the 2 and 10 mg/kg doses, the benefit–risk profile at the higher dose levels is not expected to be better than at 2 mg/kg Q3W.

The analysis supporting these conclusions represents the first comprehensive population pharmacokinetic/pharmacodynamics study of a therapy targeting PD-1/PD-L1 signaling. In this analysis, an NLME modeling framework was used to describe the relationship between systemic pembrolizumab exposure and antitumor efficacy in patients with NSCLC. The implemented model described the treatment effect on tumor size and captured kinetics of the underlying intratumoral heterogeneity of response, including the tumor shrinkage rate, underlying tumor growth for unresponsive tumor cells, and the extent to which tumors respond in an individual patient. Inclusion of *f* allowed for an empirical description of profiles in patients whose tumor size increases or stabilizes to a smaller size after an initial decrease and is coherent with the general understanding of intratumoral response heterogeneity. One could speculate that the remaining *1−f* tumor fraction may represent tumor cells with lower PD-L1 expression or poorly perfused areas of tumor inaccessible to pembrolizumab, but these hypotheses have yet to be explored.

To build the final model, a covariate search was conducted to identify factors important to NSCLC tumor growth/shrinkage patterns under pembrolizumab treatment that could be accounted for as part of the final exposure–response evaluation. In this way, the potential for imbalances and gaps in the available data to influence the exposure–response assessment was lessened, enhancing the robustness of the results. A relatively stringent significance level was used in covariate testing ($P < 0.01$ in the forward step, $P < 0.001$ in the backward step) to

(90% CI 37%–49%) at 10 mg/kg Q2W (Figure 3A). The CIs for patients with PD-L1 TPS 1%–49% also showed overlap (Figure 3B), and the relationship between k_{death} and exposure for PD-L1 TPS <1% was similarly flat (data not shown).

Table 2. Adverse event summary and duration of follow-up by dose and schedule in all patients with NSCLC treated in KEYNOTE-001 ($n = 550$)

AE, n (%)	2 mg/kg Q3W ($n = 61$)	10 mg/kg Q3W ($n = 287$)	10 mg/kg Q2W ($n = 202$)
Treatment related			
Any grade	31 (51)	201 (70)	148 (73)
Grade 3–5	5 (8)	34 (12)	19 (9)
Leading to discontinuation	4 (7)	11 (4)	8 (4)
Leading to death	1 (2)	1 (<1)	0 (0)
Immune mediated	9 (15)	39 (14)	32 (16)
Duration of follow-up, months, median (range)	8 (6–23)	16 (10–32)	16 (10–20)

AE, adverse event; Q2W, every 2 weeks; Q3W, every 3 weeks.
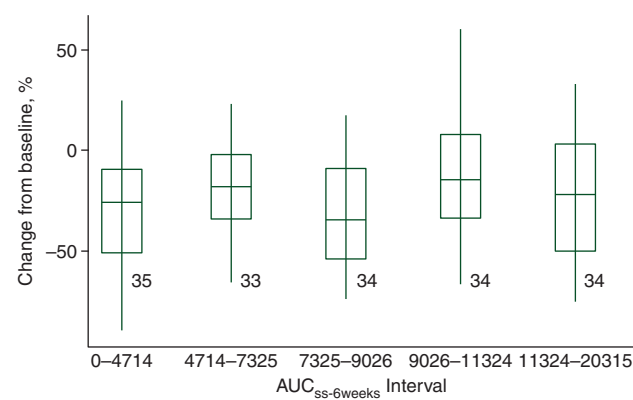
Figure 2. Observed percentage change from baseline in tumor size at 18 weeks by pembrolizumab exposure. The analysis population was patients with previously treated NSCLC who had both tumor size and exposure data at week 18 ($n = 170$). $AUC_{ss-6weeks}$ is presented in µg·day/ml. The sample size per group is shown. Lines extending vertically from the boxes (whiskers) indicate variability outside the 25th and 75th quantile. The ends of the whiskers correspond to the 5th and 95th quantiles of the observed data. All patients treated at 2 mg/kg are in the left-most bin. $AUC_{ss-6weeks}$, area under the concentration–time curve at steady state over a 6-week interval; CI, confidence interval.

mitigate the likelihood of false positives given that multiple hypothesis testing was applied during the search. Using these criteria, *EGFR* mutation and PD-L1 expression status were selected as predictors of the fraction of tumor affected by treatment and the tumor kill rate, respectively. The impact of PD-L1 and *EGFR* as predictors of tumor size kinetics is not surprising, given their established role in NSCLC cancer cell growth and the known mechanism of pembrolizumab. Aside from target lesion SLD, other factors can influence RECIST-based response assessments, including shrinkage in non-target tumors (e.g. pathologic lymph nodes) and appearance of malignant lesions indicative of disease progression. Because the model only accounted for target lesion SLD, such nuances of RECIST were not accounted for in the simulations. Therefore, caution is urged in interpreting the results and making direct comparisons with RECIST v1.1 response categories.

The efficacy profile of the 2 mg/kg Q3W dose is further supported by early translational and biomarker pharmacokinetic/pharmacodynamic results, whereby potential clinical efficacy was predicted by integrating available preclinical pharmacokinetics, PD-1 receptor occupancy and antitumor data from a syngeneic mouse model, early clinical pharmacokinetic data, and human disease properties [14]. Data from the KEYNOTE-010 study of pembrolizumab 2 and 10 mg/kg Q3W versus docetaxel for previously treated NSCLC support the similar efficacy and safety of pembrolizumab 2 and 10 mg/kg Q3W [15].

The demonstrated lack of a dose–exposure–response relationship for pembrolizumab raises the question of how to best determine the appropriate dose for immunotherapy. Recently, there has been considerable interest in optimizing dose selection for immunotherapies and other anticancer therapies [16, 17]. Currently, most oncology dose-finding studies are designed to determine the maximum tolerated dose (MTD) based on the rate of prespecified dose-limiting toxicities that occur within a prespecified period of time, usually the first treatment cycle. However, this method may be outmoded for targeted therapies and immunotherapies, for which the biologically effective dose (BED) may be much lower than the MTD [16]. Using the MTD rather than the BED could expose patients to a higher dose than that necessary to achieve clinical effect and may increase toxicity, which could lower overall clinical effectiveness. Therefore, dose determination in oncology should use a multifactorial approach that includes not only clinical data from the first treatment cycle but extended clinical data, preclinical models, pharmacokinetics, pharmacodynamics, and integrated modeling and simulation [16, 17]. Ideally, this multifactorial process would lead to a randomized dose-ranging study appropriately powered to identify the BED.

In summary, the approach reported here provides an integrated framework for exposure-efficacy analysis that accounts for imbalances in data and effects of explanatory covariates more thoroughly than those that rely exclusively on categorical end points (e.g. RECIST). The final model adequately captured the array of diverse tumor size profiles observed in the pembrolizumab-treated NSCLC population and provided strong evidence for a lack of exposure dependency on response for the clinical dose range of 2 mg/kg Q3W to 10 mg/kg Q3W/Q2W. Normalization of trial data through simulations also revealed considerable overlap of response at these dosages. Because the model-estimated exposure-slope point estimate was slightly positive, the median simulated response and upper uncertainty bounds supported the possibility that there is a modest trend of increasing response rate and decreasing stable disease rate as
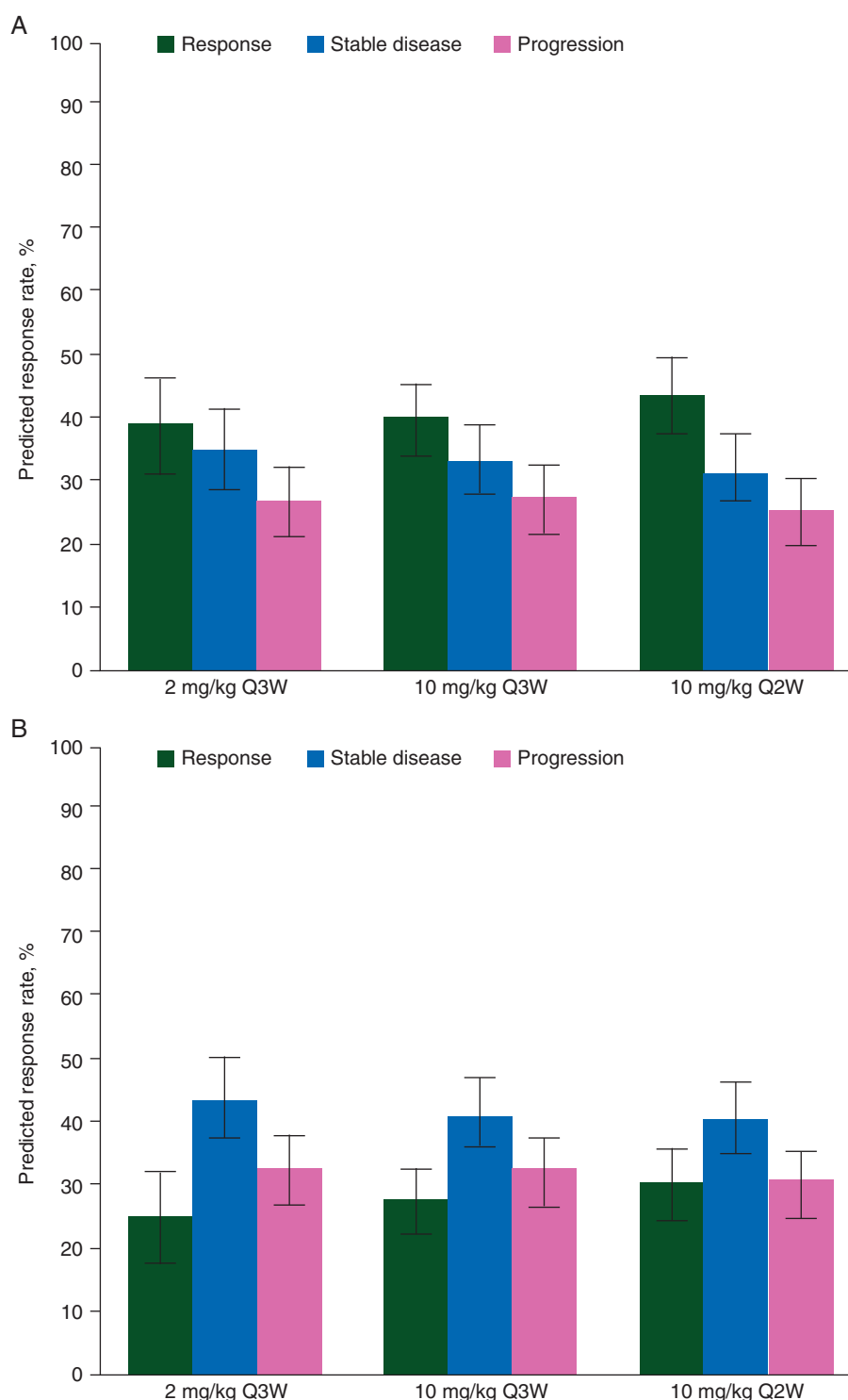
Figure 3. Median simulated response rates by pembrolizumab dose spanning the observed range of NSCLC exposure (1000 simulated trials, each with 1000 patients). (A) Patients with PD-L1 expression in ≥50% of tumor cells at week 27. (B) PD-L1 expression in 1%–49% of tumor cells at week 27. PD-L1 expression was assessed using a clinical trial immunohistochemistry assay. Error bars represent the 90% confidence intervals around the estimates. Response was defined as a ≥30% decrease from baseline in SLD, stable disease was defined as a <30% decrease but <20% increase from baseline in SLD, and progression was defined as a ≥20% increase from baseline in SLD. CI, confidence interval; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; SLD, sum of the longest diameters.

dose or frequency is increased. However, the significant overlap in CIs of the simulated response categories across a wide spectrum of exposures suggests antitumor response is likely saturated in this dose range. Therefore, it is likely that between-patient differences in pembrolizumab pharmacokinetics do not result in clinically relevant differences in efficacy over the dose

range of 2 mg/kg Q3W to 10 mg/kg Q2W. Overall, the clinical data and model-based statistical testing and trial simulations of the magnitude of the exposure–response relationship support 2 mg/kg Q3W as an appropriate dose for pembrolizumab in patients with NSCLC.

disclosures

EBG reports funding to the institution from Merck for conduct of the study. MAG reports the following disclosures outside the submitted work: personal fees from Boehringer Ingelheim, Bristol-Myers Squibb, Calithera, Clovis, and Pfizer for serving as an advisory board member; grants from Abbvie, Celgene, Genentech/Roche, Merck, Novartis, and OncoMed for serving as the principal investigator of clinical trials; and non-financial support from Celgene and Genentech/Roche for serving as an advisory board member. MDH reports funding to the institution from Merck for conduct of this study and, outside the submitted work, grant support from Bristol-Myers Squibb and personal fees from AstraZeneca, Genentech, Inovio, and Neon. LH reports personal fees from Merck for serving as an advisory board member and, outside the submitted work, personal fees from Genentech for serving as an advisory board member; personal fees from Biodesix for serving as a speaker; and serving as an uncompensated consultant for Bayer, Bristol-Myers Squibb, and Xcovery. RH reports the following disclosures outside the submitted work: personal fees from Merck Sharp & Dohme for serving as an advisory board member and speaker; personal fees from AstraZeneca for serving as an advisory board member and consultant; personal fees from Pfizer for serving as an advisory board member; and personal fees from Boehringer Ingelheim and Roche for serving as a speaker. HL reports the following disclosures outside the submitted work: grant support, personal fees, and non-financial support from Roche; personal fees and non-financial support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, and Pierre Fabre Oncologie; personal fees from Novartis; and non-financial support from Amgen. MA, MC, DPDA, DD, TF, EI, AGK, CL, GML, KM, JS, DCT, and JZ are full-time employees of and may hold stock options in Merck & Co., Inc. (Kenilworth, NJ, USA). H-TA, FC, EF, and ØF report nothing to disclose.

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